PPCPs in the Environment: an Overview of the Science

Christian G. Daughton, Ph.D.

Chief, Environmental Chemistry Branch

Environmental Sciences Division

National Exposure Research Laboratory

Office of Research and Development

Environmental Protection Agency

Las Vegas, Nevada 89119

daughton.christian@epa.gov

Although this work was reviewed by the U.S. Environmental Protection Agency (EPA) and approved for presentation, it may not necessarily reflect official Agency policy. While the text for this presentation has been reviewed, the oral narrative has not. Mention of trade names or commercial products does not necessarily constitute endorsement or recommendation by EPA for use.

Other materials and links are available at the

U.S. EPA's ***<u>PPCPs Web Site</u>***:

http://www.epa.gov/nerlesd1/chemistry/pharma

Historical Perspective - PPCPs

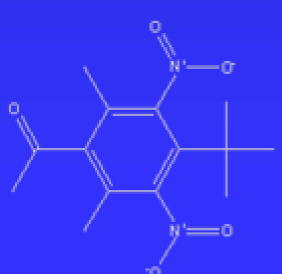
- PPCPs as environmental pollutants first investigated in Europe - 1980s.
- With the advent of monitoring and research in the U.S., literature has grown exponentially since 2000.
- PPCPs are not truly "emerging" pollutants. It is the understanding of the significance of their occurrence in the environment that is beginning to develop.
- Topic has high public visibility.
- Continues to attract significant media attention - newspapers, magazines (popular, trade, and science), radio, and TV.
- Overall issue comprises numerous facets involving expertise from a broad spectrum of disciplines ranging from human health to ecology - - necessitating communication between the medical/healthcare communities and environmental scientists.

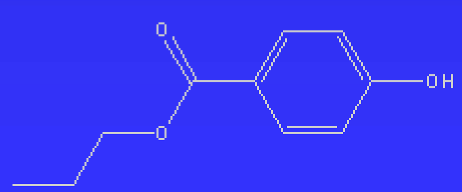
Scope of Issue

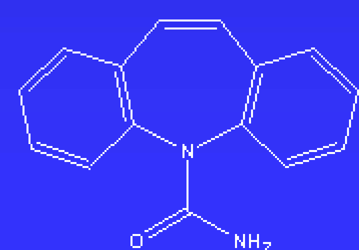
- Thousands of distinct chemical entities.
- Numerous (and increasing) therapeutic classes and end uses.
- Large numbers possess very high biological activity.
- Two classes of therapeutics that have received the most attention are the antibiotics (potential for resistance selection among pathogens) and steroidal hormones (overlap with EDCs).
- For the plethora of other classes, however, little is known regarding the potential for effects.
- In general, PPCPs are not regulated water pollutants.
- Regulated pollutants compose but a very small piece of the universe of chemical stressors to which organisms can be exposed on a continual basis.

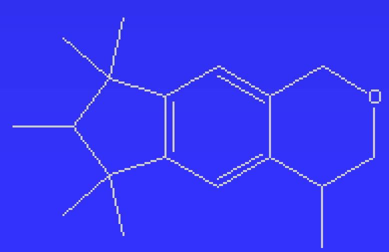
PPCPs as Environmental Pollutants?

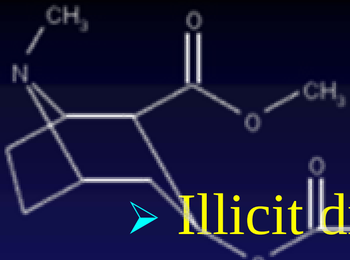
PPCPs are a diverse group of chemicals comprising all human and veterinary drugs (available by prescription or OTC; including biologics” and illicit drugs), diagnostic agents (e.g., X-ray contrast media), “nutraceuticals” (bioactive food supplements such as huperzine A), functional foods (“phoods” and “bepherages”), and other consumer chemicals, such as fragrances (e.g., musks) and sun-screen agents (e.g., 4-methylbenzylidene camphor; octocrylene); also included are “excipients” (so-called “inert” ingredients used in PPCP manufacturing and formulation; e.g., parabens).

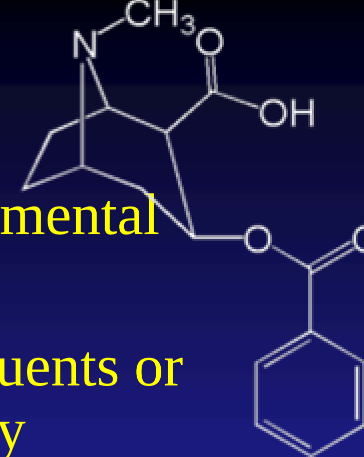












Illicit Drugs as Pollutants?

- Illicit drugs pose the same issues with respect to environmental exposure as ~~do~~ therapeutic drugs.
- In addition, by monitoring their presence in sewage effluents or surface streams, they can play a valuable role in objectively measuring community-wide drug usage.
- Revolutionary approach was conceptualized for empirically measuring societal usage of illicit and abused drugs by in-stream monitoring of unique metabolites (Daughton 2001). This work led to the first monitoring-based estimate of cocaine use (Zuccato et al. 2005), where calculations using field data showed usage in Italy exceeded official questionnaire-based estimates by several fold.

Daughton 2001 "Illicit Drugs in Municipal Sewage: Proposed New Non-Intrusive Tool to Heighten Public Awareness of Societal Use of Illicit/Abused Drugs and Their Potential for Ecological Consequences," in C.G. Daughton and T.L. Jones-Lepp (Editors), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, Symposium Series 791, American Chemical Society: Washington, D.C., 2001, pp. 348-364; available: http://epa.gov/nerlesd1/chemistry/pharma/book-conclude.htm.

Zuccato et al. 2004 "Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse," Environmental Health: A Global Access Science Source, 4(14): 1-7.

Origins of PPCPs in the Environment

- Portions of most ingested drugs are excreted in varying unmetabolized amounts (and in undissolved states because of protection by excipients) primarily via the urine and feces.

- Other portions sometimes yield metabolites that are still bioactive. Still other portions are excreted as conjugates.

- Free excreted drugs and derivatives can escape degradation in municipal sewage treatment facilities (removal efficiency is a function of the drug's structure and treatment technology employed); the conjugates can be hydrolyzed back to the free parent drug.

- Un-degraded molecules are then discharged to receiving surface waters or find their way to ground waters, e.g., leaching, recharge.

Origins of PPCPs in the Environment

- Other potential routes to the environment include leaching from municipal landfills, runoff from confined animal feeding operations (CAFOs) and medicated pet excreta, loss from aquaculture, spray-drift from agriculture, direct discharge of raw sewage (storm overflow events & residential “straight piping”), sewage discharge from cruise ships (millions of passengers per year), illegal “clan” labs (especially methamphetamine), oral contraceptives used as soil amendment and plant growth tonic (urban legend), and transgenic production of proteinaceous therapeutics by genetically altered plants (aka “molecular farming” — “biopharming”).

- Direct discharge to the environment also occurs via dislodgement/washing of externally applied PPCPs.

PPCPs as "Emerging" Risks?

It is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. It has only become more widely evident in the last decade because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. **There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.**

The Confusing Terminology of Chemical Pollutant Classes

Class or Grouping	Grouped According to:
EDC (Endocrine Disrupting Chemical) **CMR** (Carcinogenic, Mutagenic, toxic to Reproduction)	toxicological mode of action or endpoint
PBT (Persistent, Bioaccumulative Toxic) **vPvB** (very Persistent, very Bioaccumulative) **POP** (Persistent Organic Pollutant)	environmental properties
micro-pollutants; **micro-constituents** **trace pollutants/residues**	frequency/level of occurrence
OWCs (Organic Wastewater Contaminants)	location of occurrence
PPCPs (also PhACs, which is a subset)	type of intended usage
priority pollutants and others	regulation
unregulated pollutants	absence of regulation
“chemical weeds”	public perception ("out of place chemicals")
emerging contaminants/pollutants **EPOCs** (emerging pollutants of concern) **COCs** (chemicals of concern) **COPCs** (chemicals of potential concern) **CECs** (chemicals of emerging concern)	novelty, fad, timeliness, or new concern
xenobiotics, exotics **xenobiotic organic compounds (XOCs)**	foreign versus endogenous
toxicants, toxins, toxics, perturbogens (agonists, antagonists, activators, repressors, inhibitors, regulators, modulators)	overall toxicity (*note*: "toxins" comprise a special subset of toxicants - those naturally synthesized, primarily proteins; "toxics" is jargon for "toxicants")
HPV (high production volume) chemicals	quantity (manufactured/imported in US ≥1 million pounds/year)
PDPs or **HDPs** (population- or human-derived pollutants/constituents) **POHO** (pollutants of human origin)	source or origin

Adapted and extended by Daughton from: *Renewable Resources Journal*, 2005, 23(4):6-23.

"Emerging Pollutants": Relatively New Topic of the Published Literature

"Emerging Pollutants" — Questions, Challenges, and the Future (CG Daughton)
[published in: *Norman Newsletter* (Network of Reference Laboratories for Monitoring of Emerging Environmental Pollutants), Issue #1, June, 2006]
http://www.norman-network.net/newsletters/newsletter_norman_1.pdf

"Emerging" Chemicals as Pollutants in the Environment: a 21st Century Perspective (CG Daughton)
[published in: *Renewable Resources Journal*, 2005, 23(4):6-23]

Environmental Impacts of Emerging Contaminants (CG Daughton)
http://www.rnrf.org/2005cong/

[published in: *Renewable Resources Journal*, Spring 2006, 24(1), 35 pp; final report from the Renewable Natural Resources Foundation's Congress on Assessing and Mitigating Environmental Impacts of Emerging Contaminants, Washington, D.C., 1-2 December 2005]

Non-Regulated Water Contaminants: Emerging Research (CG Daughton)
[published in: *Environmental Impact Assessment Review* 2004, 24(7-8):711-732]
http://epa.gov/nerlesd1/chemistry/pharma/images/EIAR.pdf

Emerging Substances—Emerging Problems? (PM Chapman)
[published in: *Environmental Toxicology and Chemistry*, 2006, 25(6):1445–1447]

NORMAN (Network of Reference Laboratories for Monitoring of Emerging Environmental Pollutants (**http://www.norman-network.net/index_php.php**). Project funded under the EU's 6th Framework Programme. Major objective to bring together scientists engaged in environmental monitoring to discuss approaches for coordinating the study and monitoring of the so-called "emerging" pollutants.

“PBTs” - “POPs” - “BCCs”: Only one part of the risk puzzle?

Since the 1970s, the impact of chemical pollution has focused almost exclusively on conventional “priority pollutants”†, especially on those collectively referred to as “persistent, bioaccumulative, toxic” (PBT) pollutants, “persistent organic pollutants” (POPs), or “bioaccumulative chemicals of concern” (BCCs).

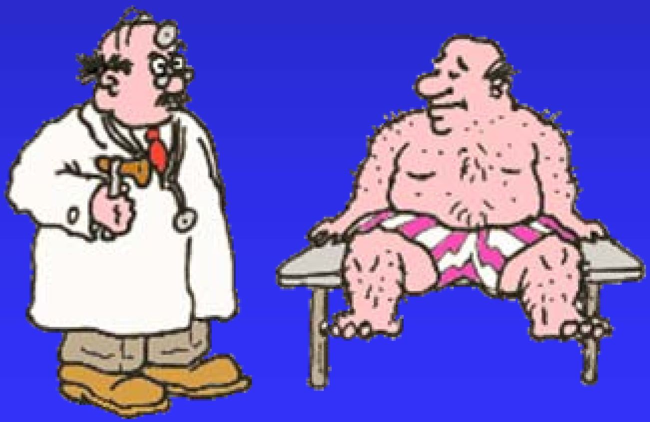
The “dirty dozen” is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

The conventional priority pollutants, however, are only one piece of the larger risk puzzle.

† an historical note: the current “lists” of priority pollutants were originally established in the 1970s in large part based on which chemicals of initial concern could be measured with off-the-shelf chemical analysis technology. Priority pollutants were NOT selected because they posed the sole risks.

What portion of overall risk is contributed by unregulated pollutants?

Can risk be assessed in a truly holistic manner without knowing the actual exposure universe?



The Chemical Universe

The *KNOWN* Universe

- As of April 2007, roughly 31 million organic and inorganic substances had been documented.

(indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry; excluding bio-sequences such as proteins and nucleotides)

- Of these nearly 31 million known chemicals, nearly 14 million were commercially available.
- Representing a 40% increase over the prior year.
- Of these, fewer than a quarter million (245,000) were inventoried or regulated by numerous government bodies worldwide - - representing less than 1.8% of those that are commercially available or less than 0.8% of the known universe of chemicals.

http://www.epa.gov/nerlesd1/chemistry/pharma/critical.htm

The Chemical Universe

The *POTENTIAL* Universe

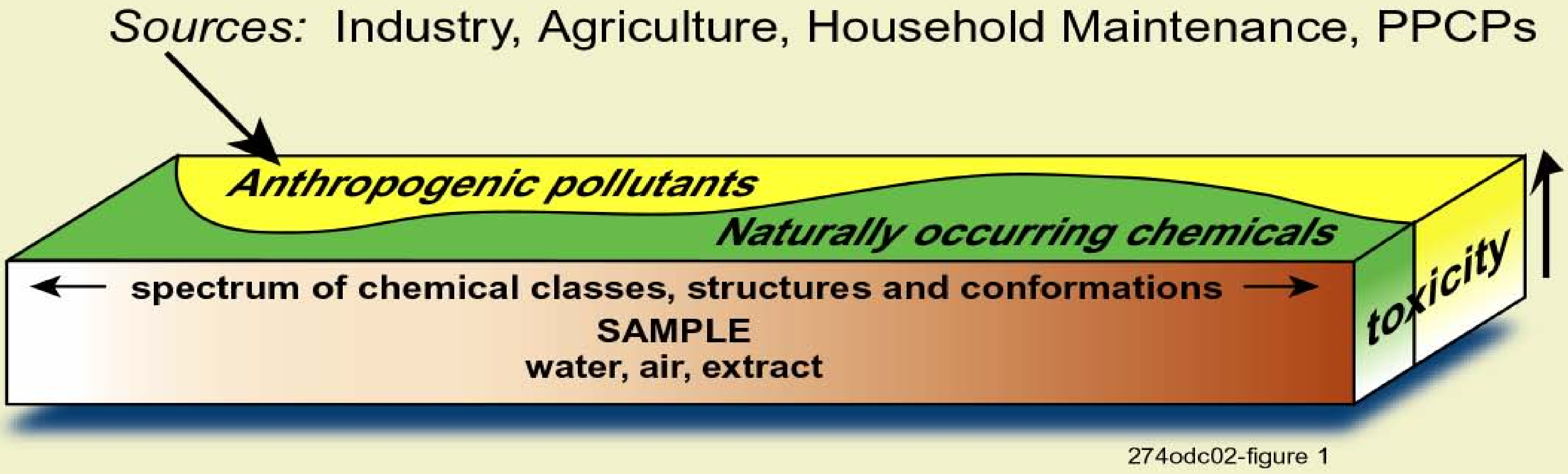
- While the *KNOWN* universe of chemicals might seem large (32 million), the universe of *POTENTIAL* chemicals (those that could possibly be synthesized and those that already exist but which have not yet been identified) is unimaginably large.

How many distinct organic chemical entities could hypothetically be synthesized and added to a seemingly limitless, ever-expanding chemical universe?

- By limiting synthesis strictly to combinations of 30 atoms of just C, N, O, or S, **more than 10^{60} structures are possible !**

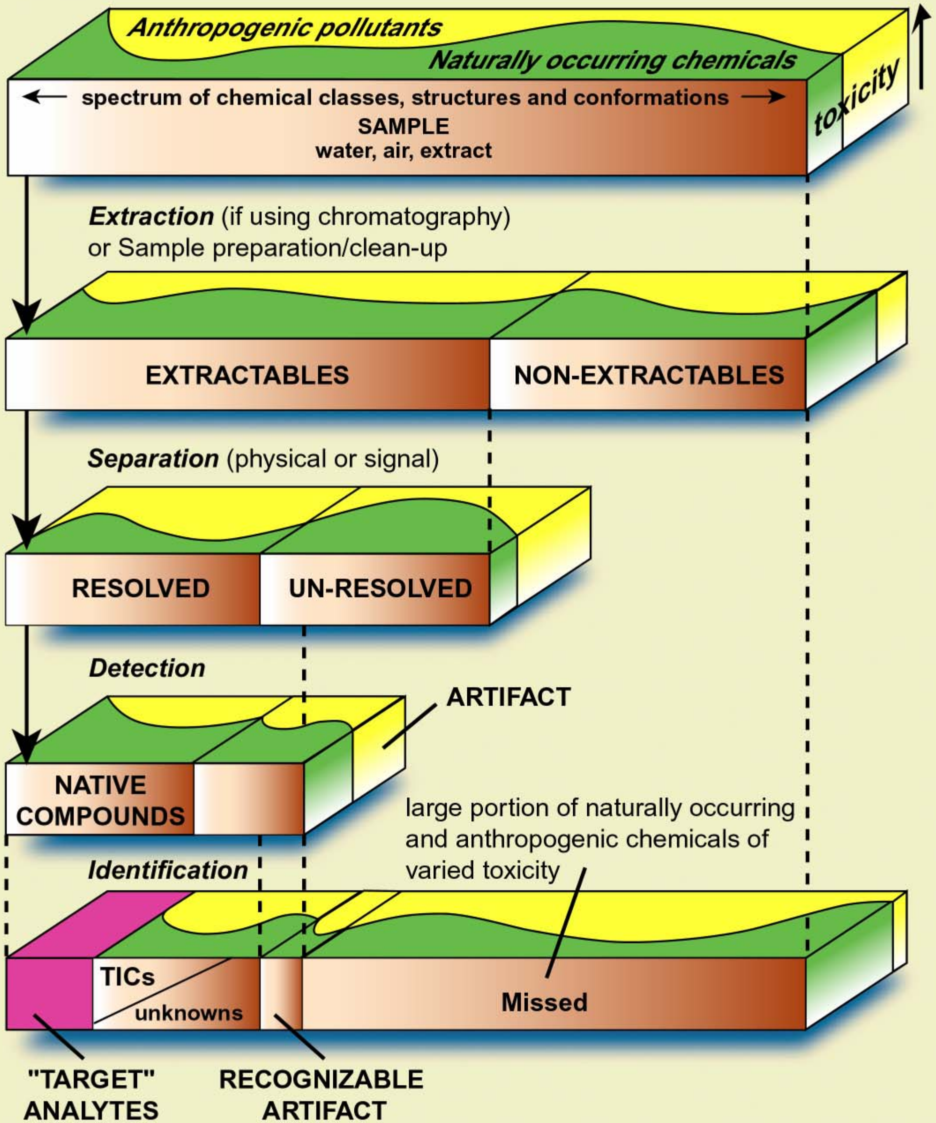
- Expanding the allowable elements to other heteroatoms (e.g., P and halogens), the limits to the numbers of possible structures defies imagination. Also known as "chemical space".

Universe of Chemicals in the Environment



For more discussion, see:
http://epa.gov/nerlesd1/chemistry/pharma/critical.htm

Limitations and Complexity of Environmental Chemical Analysis

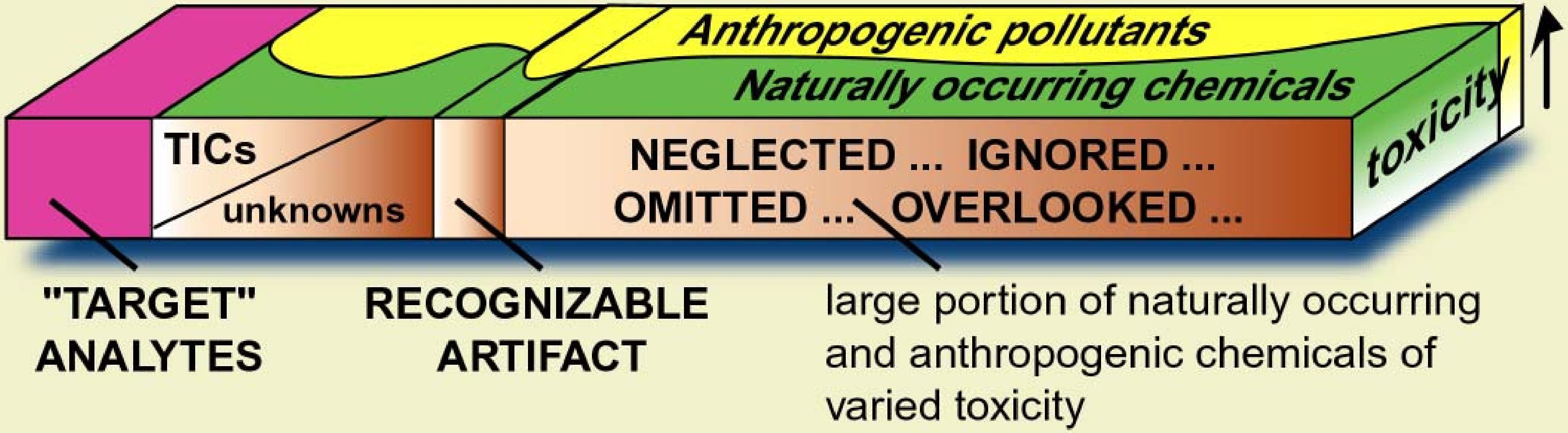


TICs = tentatively identified compounds

C.G. Daughton
U.S. EPA July 2002

274odc02-figure 2

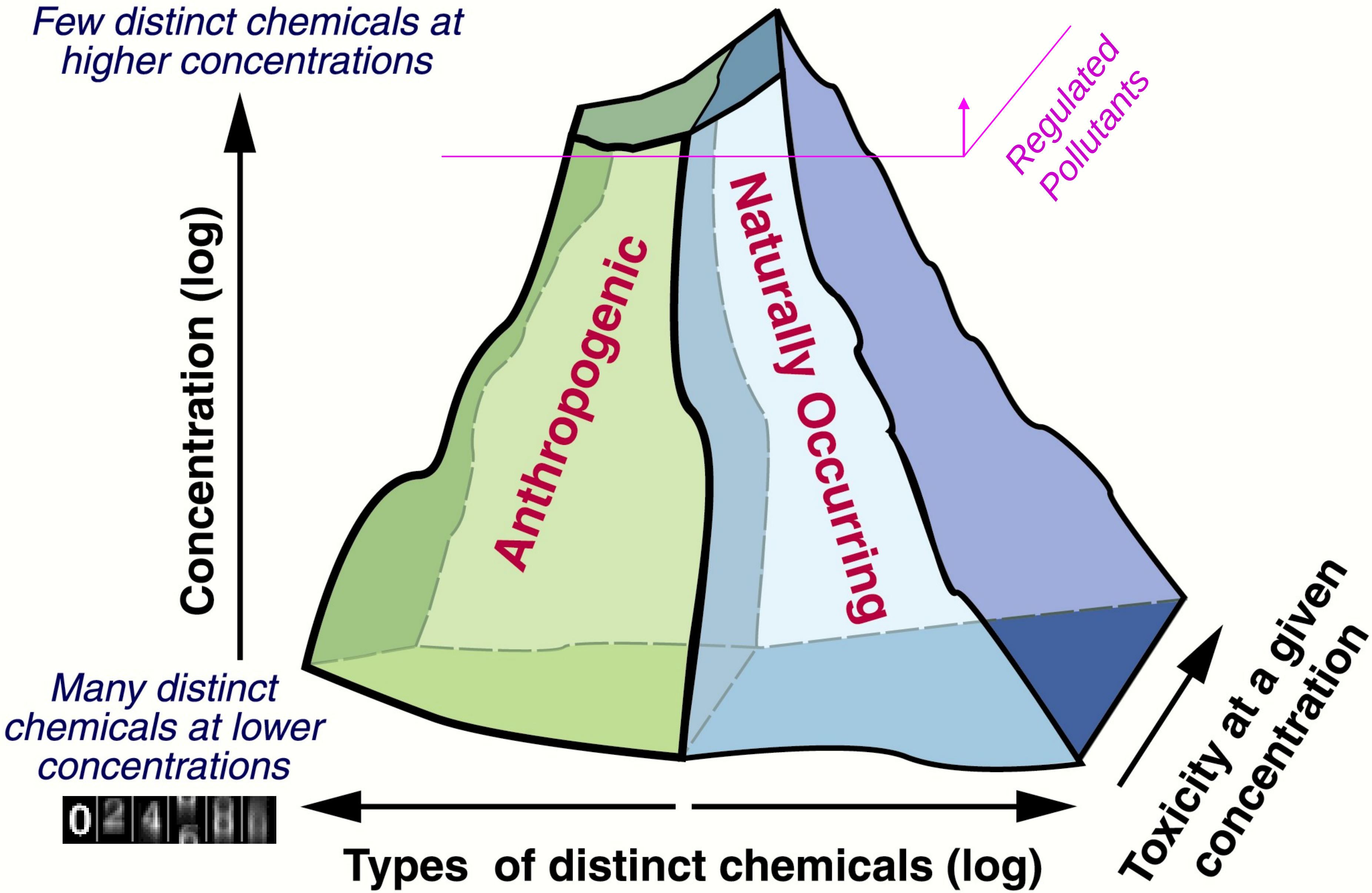
Chemical Analysis Output for a Typical Environmental Sample



TICs = tentatively identified compounds

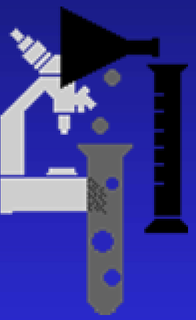
C.G. Daughton
U.S. EPA July 2002

Prevalence/Distribution of Xenobiotic Occurrence



Einstein on:
Environmental Monitoring

"Not everything that can be counted counts, and not everything that counts can be counted." (oft attributed to Albert Einstein)

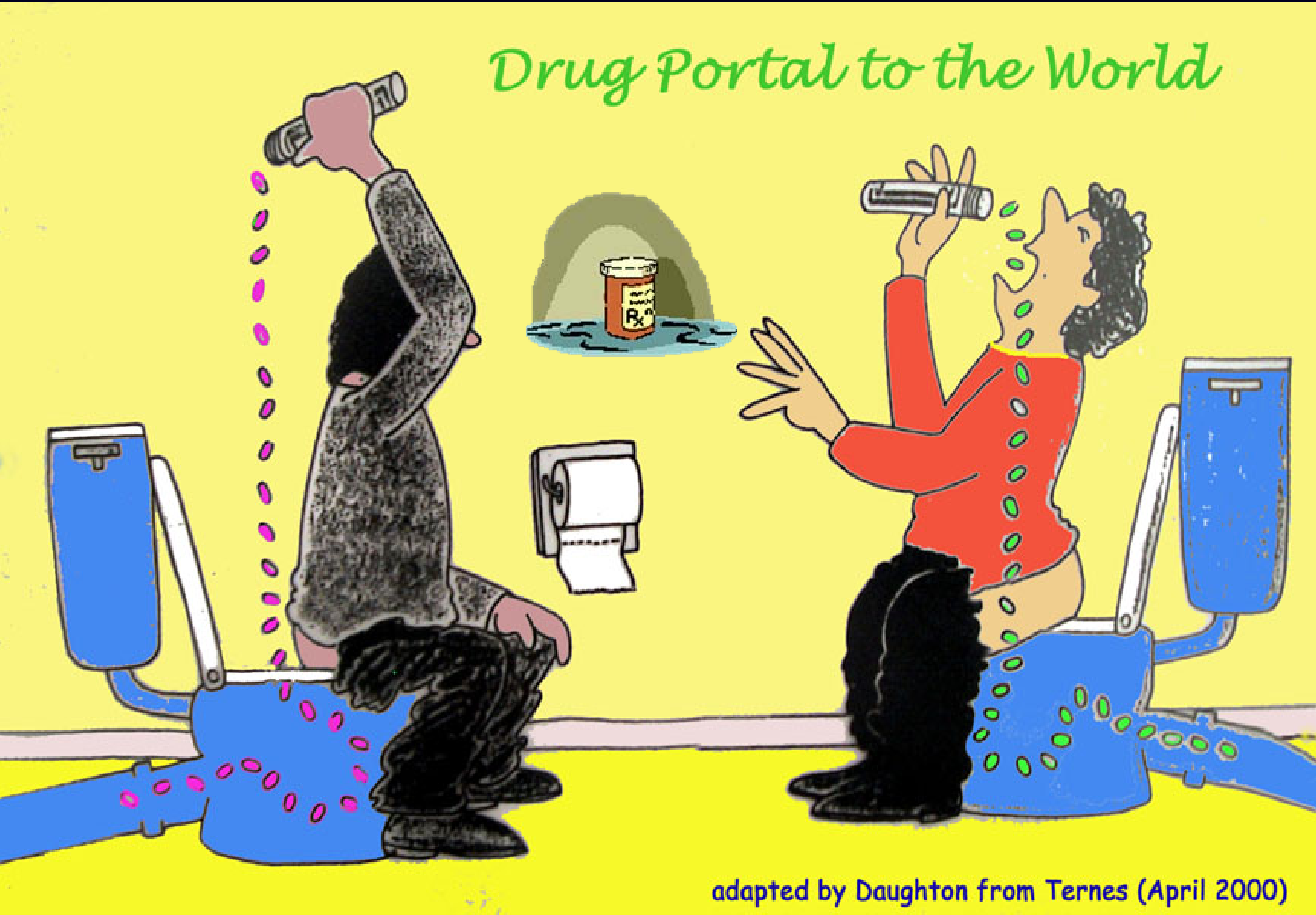


corollary for environmental monitoring

Not everything that can be measured is worth measuring, and not everything worth measuring is measurable.

further truisms regarding *Environmental Monitoring*

- What one finds usually depends on what one aims to search for.
- Only those compounds targeted for monitoring have the potential for being identified and quantified.
- Those compounds not targeted will elude detection.
- The spectrum of pollutants identified in a sample represent but a portion of those present and they are of unknown overall risk significance.


Drug Portal to the World
Rx
adapted by Daughton from Ternes (April 2000)

Inter-Connectedness of Humans and the Environment

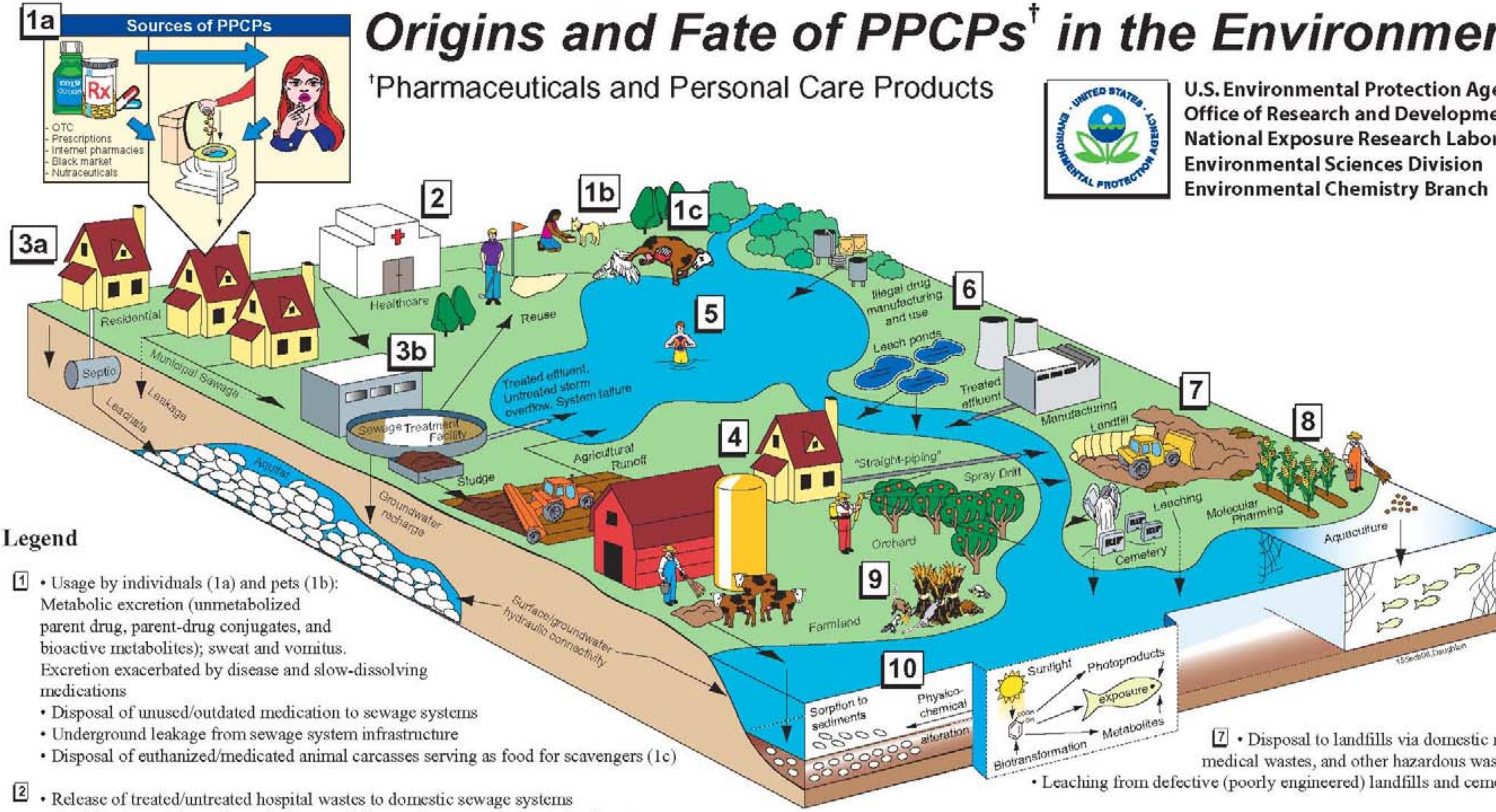
- Occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the actions and activities of individuals and their environment.

- PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals.

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch



Legend

1 • Usage by individuals (1a) and pets (1b): Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus. Excretion exacerbated by disease and slow-dissolving medications
• Disposal of unused/outdated medication to sewage systems
• Underground leakage from sewage system infrastructure
• Disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)

2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus

3 • Release to private septic/leach fields (3a)
• Treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b)
• Overflow of untreated sewage from storm events and system failures directly to surface waters (3b)

4 • Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
• "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
• Release from agriculture: spray drift from tree crops (e.g., antibiotics)
• Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)

5 • Direct release to open waters via washing/bathing/swimming

6 • Discharge of regulated/controlled industrial manufacturing waste streams
• Disposal/release from clandestine drug labs and illicit drug usage

7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
• Leaching from defective (poorly engineered) landfills and cemeteries

8 • Release to open waters from aquaculture (medicated feed and resulting excreta)
• Future potential for release from molecular pharming (production of therapeutics in crops)

9 • Release of drugs that serve double duty as pest control agents: examples: 4-aminopyridine, experimental multiple sclerosis drug → used as avicide; warfarin, anticoagulant → rat poison; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → *coqui* frog control

10 Ultimate environmental transport/fate:
• most PPCPs eventually transported from terrestrial domain to aqueous domain
• phototransformation (both direct and indirect reactions via UV light)
• physicochemical alteration, degradation, and ultimate mineralization
• volatilization (mainly certain anesthetics, fragrances)
• some uptake by plants
• respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

Christian G. Daughton, U.S. EPA-Las Vegas

March 2006
(original February 2001)

http://epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf
from: http://epa.gov/nerlesd1/chemistry/pharma/

Ramifications

- Exposure at therapeutic doses is NOT the concern.
- Exposure to non-target organisms could be significant.
- Continual input via treated sewage imparts PPCPs with "pseudo-persistence" even if they have short half-lives.
- Aquatic organisms can suffer continual exposure.
- Potential exists for subtle effects (e.g., neurobehavioral change), even at ppb levels (µg/L).
- Potential exists for inhibition of aquatic defensive mechanisms such as efflux pumps.
- Pose many challenges for the outer envelope of toxicology - especially the many unknowns associated with effects from simultaneous exposure to multiple chemical stressors over long periods of time.
- Potential for additive (cumulative) and interactive (synergistic) effects from multiple exposure.

Toxicity of
Complex Environmental Mixtures:
Poses Major Unanswered Questions

Exposure to Multiple, Trace-Level Xenobiotics below Known Effects Levels

Potential Toxicological Significance as a Result of:

(1) Potential for **additive effects** from multiple agents sharing common mechanisms action (MOAs). Individual concentrations combine to exceed an effects level.

(2) Possible **interactive effects**, especially synergism, where combined action exceeds the sum of individual effects.

(3) **Hormesis** – Effects below purported NOELs. Paradoxical "U-shaped" dose-response curves.

continued >

Potential Toxicological Significance as a Result of:

(4) Dynamic Dose-Response. **Toxicant-Induced Loss of Tolerance (TILT)**: initial exposure sensitizes, and subsequent exposures to levels below those previously tolerated trigger symptoms (e.g., ecological version of MCS or chemical hyperreactivity).

(5) Comparatively little research performed at **extremely low concentrations** (nM-pM and below). Some agents have ability to impart previously unrecognized effects at "ultra-trace" concentrations.

(6) **Non-target species receptor repertoires** not well characterized. Variation in receptor repertoires across species, and unknown overlap with humans leads to countless questions regarding potential effects.

continued >

Potential Toxicological Significance as a Result of:

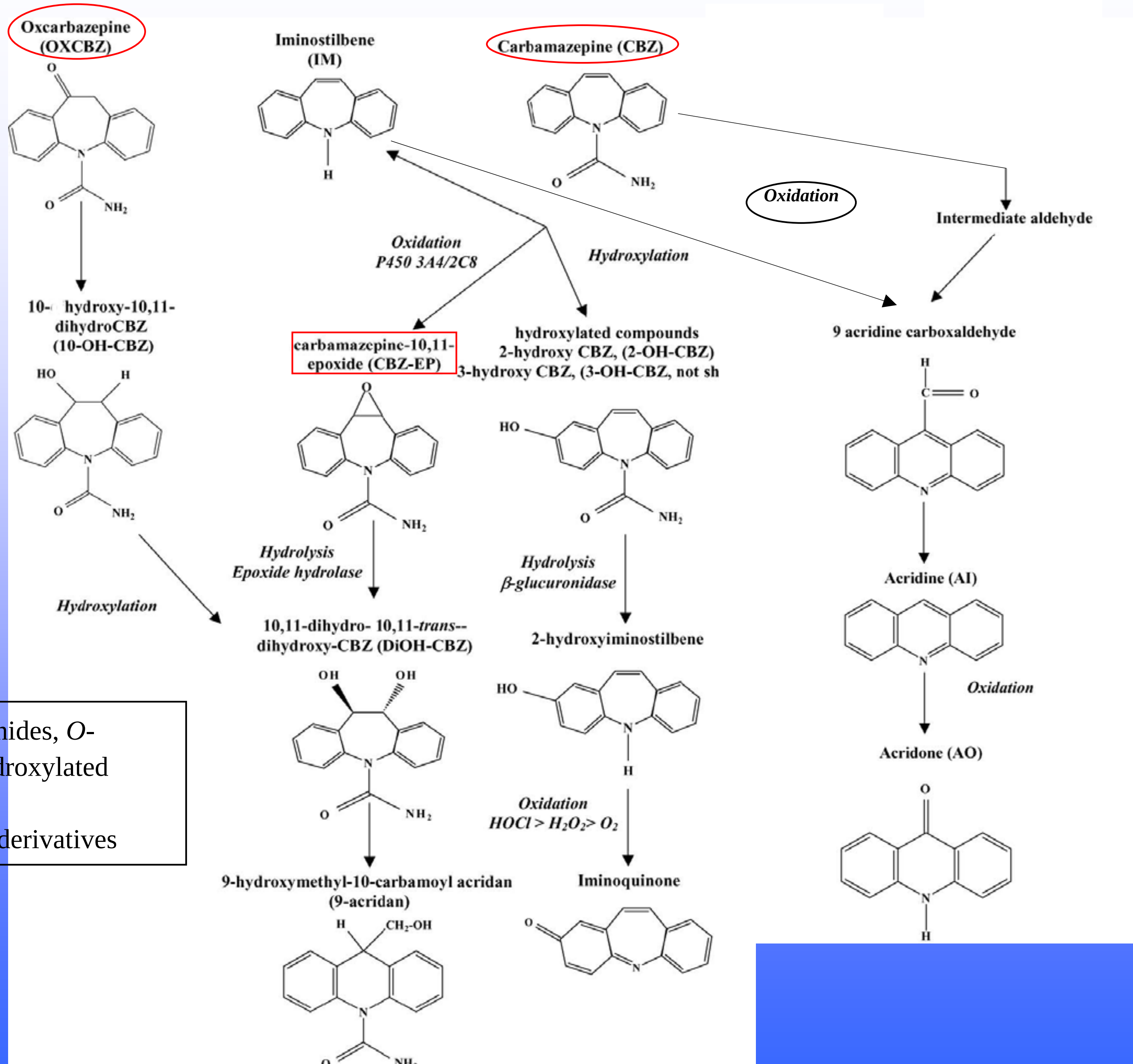
(7) Susceptible **genetic outliers** within species.

(8) **MOAs not fully understood**. Even most drugs can each have a multitude of effects. Most MOAs for the therapeutic endpoints, however, remain to be discovered, even for humans.

(9) **Dose-dependent transitions in MOAs** (multi-phasic dose-response curves resulting from shifts in the MOA over the dose continuum)

- concluded -

Carbamazepine & Oxcarbazepine: *Complex Metabolism*



Multitude of *N*-glucuronides, *O*-conjugates (of monohydroxylated derivatives), and methylsulfinylhydroxy derivatives

Adapted from: H. Breton et al., *J. Chromatogr. B*, 2005, 828(1-2):80-90.

Pharmacokinetics and Predicting Environmental Fate

Using carbamazepine (CBZ) as but one example, the following generalities emerge:

- Pharmacokinetics essential to understand complexity of metabolites that can be excreted [CBZ has at least 30 different human metabolites].

- Wide spectrum of metabolites can be created from a single active ingredient.

- Many of these metabolites are excreted and can become pollutants themselves.

- Excreted conjugates can serve as hidden reservoirs of the parent chemical if they are subsequently hydrolyzed (e.g., by microbial activity).

- Extensively metabolized drugs such as CBZ (less than 3% is excreted unchanged in the urine) can nonetheless persist in the environment.

- Pharmacokinetics is not necessarily a predictor of waste treatment efficacy. CBZ is an example - - extensively metabolized by humans but relatively refractory to microbial degradation in waste treatment and in the environment.

PPCPs in Receiving Waters: A Global, Ubiquitous Process with Unique Local Expression

- Important to recognize that ALL municipal sewage, regardless of location, will contain PPCPs. Issue is not unique to any particular municipal area.

- Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs.

Aquatic organisms — captive to continual, life-cycle chemical exposures

- Aquatic Exposure is Key: Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.

- Re-evaluation of "Persistence":
Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat). These can be referred to as ***pseudo-persistent* chemicals (P2's)**.

PPCPs in Biosolids

- In the absence of mass balances, the mechanisms of waste treatment removals of PPCPs from the aqueous effluent cannot be deduced.

- Significant portions of certain PPCPs partition to the sludge and remain stable in biosolids products; levels can reach the mg/kg (ppm) level.

- Jones-Lepp TL, Stevens R "Pharmaceuticals and Personal Care Products in Biosolids/Sewage Sludges - The Interface between Analytical Chemistry and Regulation," Analytical and Bioanalytical Chemistry, accepted 2006.
- Heidler J, Sapkota A, Halden, RU "Partitioning, Persistence, and Accumulation in Digested Sludge of the Topical Antiseptic Triclocarban During Wastewater Treatment," Environmental Science and Technology, 2006, 40(11):3634-3639.
- Heidler J, Halden RU "Mass Balance Assessment of Triclosan Removal During Conventional Sewage Treatment," Chemosphere, in press 2006 (available online 12 June 2006).
- Kinney CA, Furlong ET, Zaugg SD, Burkhardt MR, Werner SL, Cahill JD, Jorgensen GR "Survey of Organic Wastewater Contaminants in Biosolids Destined for Land Application," Environmental Science and Technology, in press 2006 (available online 13 September 2006).
- Osemwengie LI "Determination of Synthetic Musk Compounds in Sewage Biosolids by Gas Chromatography/Mass Spectrometry," Journal of Environmental Monitoring, 2006 , 8(9):897-903.
- Harrison EZ, Oakes SR, Hysell M, Hay A "Organic Chemicals in Sewage Sludges," Science of the Total Environment, 2006, 367(2-3):481-497; available: http://cwmi.css.cornell.edu/sludge/organicchemicals.pdf (review involving pollutants in general)

PPCPs as Exposure Sources for Conventional Pollutants

- Ayurveda and folk remedies (e.g., litargirio, or litharge): **lead (Pb)** and other metals (upwards of 80% by weight)
- Skin lightening creams and disinfectant soaps (imported): upwards of 3% **mercuric iodine** (wt/wt) in soaps and 10% **ammoniated mercury** in skin lightening creams
- Dermal products: **phthalates** (esp. diethyl and dibutyl), **solvents**, **dyes**, **parabens** (4-hydroxybenzoic acid alkyl esters), **cyclosiloxanes** (e.g., octamethylcyclotetrasiloxane, D4)
- Lice and tick control shampoos: **lindane** and **permethrins**
- Shampoos and soaps: **alkylphenolic surfactants**
- Chemical-impregnated clothing: **permethrins** for repelling insects
- Metered-Dose inhalers (e.g., for asthma): chlorofluorocarbons used as propellants (EPA allowed use of 1,002 metric tonnes in 2006 through health exemption to the Montreal Protocol)

Potential for Subtle Effects?

continued >

Potential for Subtle (currently unrecognized) Effects?

- Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time? For example, latent damage, only surfacing later in life. The issue of “resiliency”.

- Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause?

- Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological) — e.g., subtle shifts in behavior or intelligence.

- Advances required in developing/implementing new aquatic toxicity tests to better ensure that such effects can be detected.

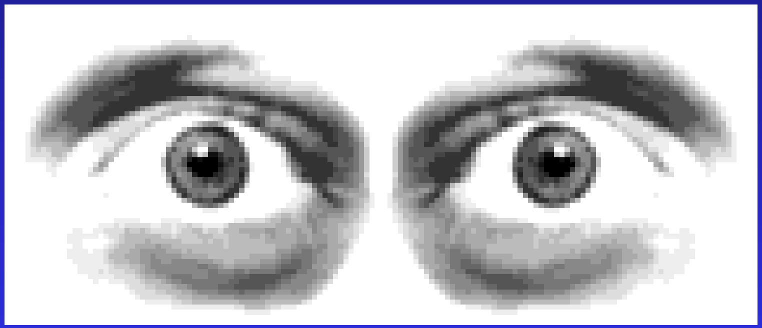
continued >

Potential Subtle, Difficult-to-Detect Effects:

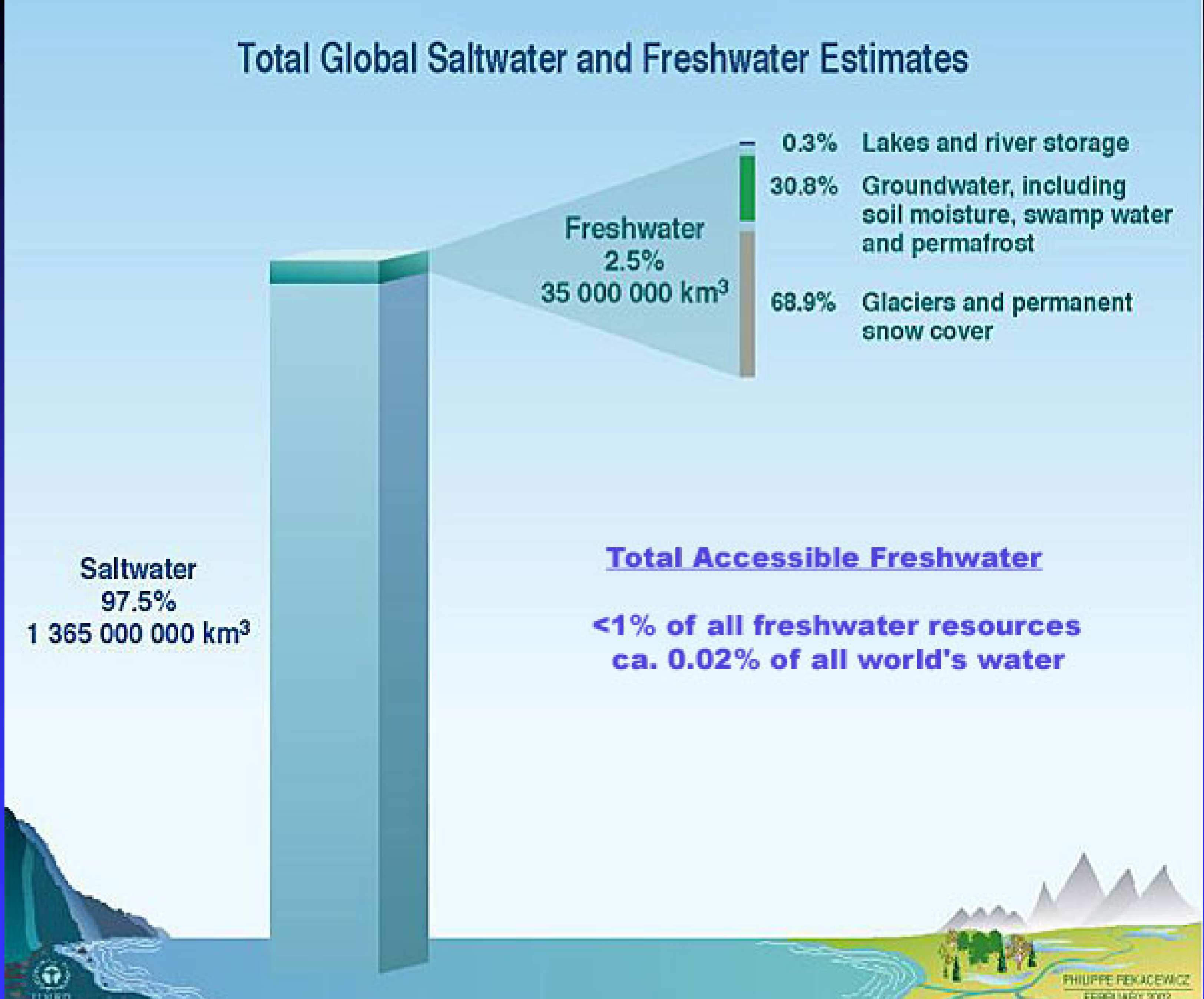
some examples

- Profound effects on development, spawning, and wide array of other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants (ppb levels).
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of efflux pump inhibitors in compromising aquatic health?

Peeking at the Future



The World’s Accessible Freshwater Resources



Source: Igor A. Shiklomanov, State Hydrological Institute (SHI, St. Petersburg) and United Nations Educational, Scientific and Cultural Organisation (UNESCO, Paris), 1999.

Which water would you choose ?
Recycled Sewage or Snow Melt ?

"Clean" water depends on one's perspective ...

San Francisco Exploratorium

A Sip of Conflict -or- *The Conflicted Sip*

Key to Maintaining & Improving the Public's Confidence in Water Supplies

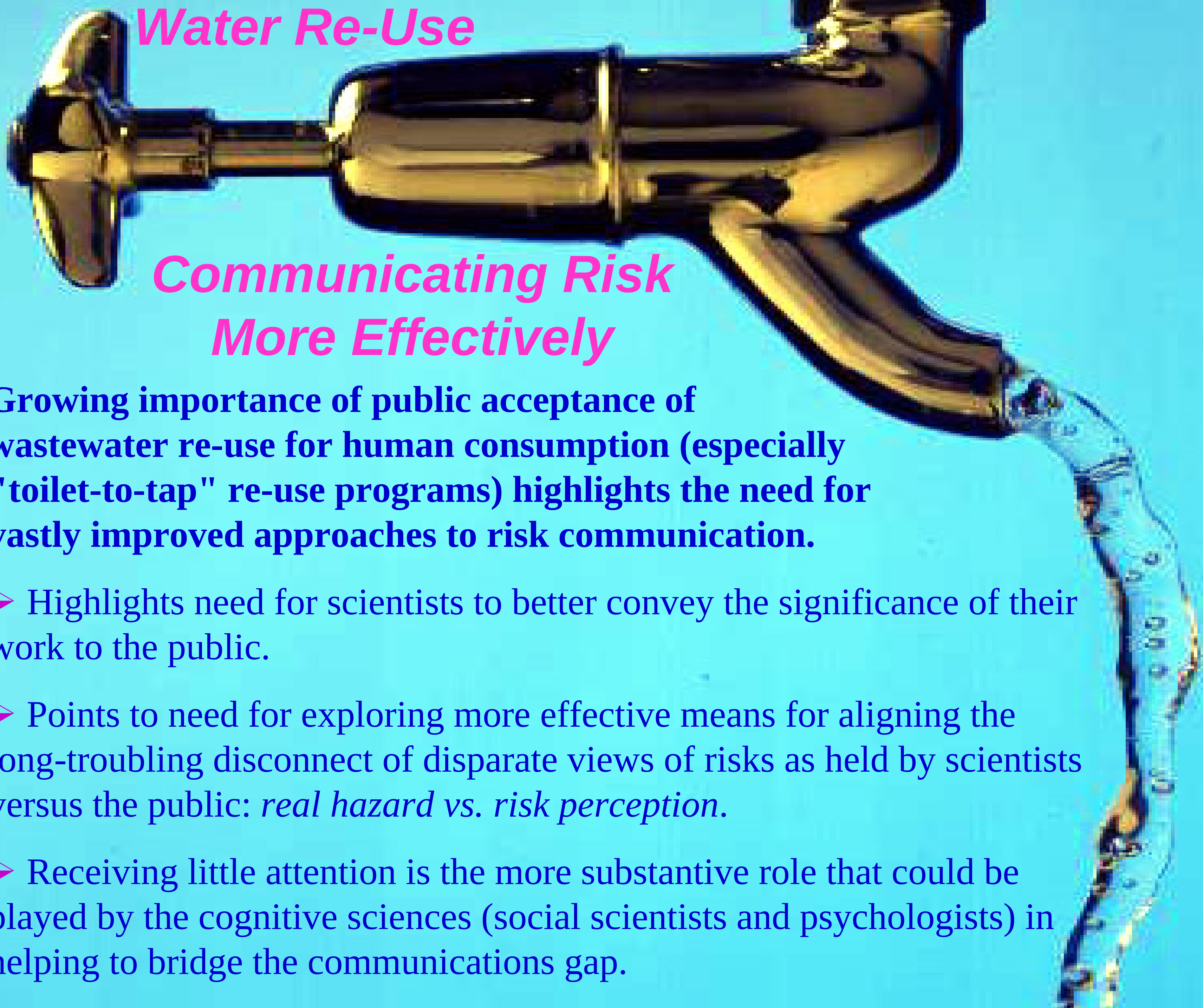
Growing pressures to re-use wastewaters for drinking

"Increasingly Smaller Recycle Loops": Ever-shortening spatial & temporal hydraulic connectivity between point of wastewater discharge and point of use for drinking will pose serious challenges for ensuring human safety and for framing how risk is perceived by the consumer.

Two Major Issues:

Groundwater Recharge (both indirect and direct)

De-Centralized Water Re-Use - - "Toilet-to-tap"



Water Re-Use

Communicating Risk More Effectively

Growing importance of public acceptance of wastewater re-use for human consumption (especially "toilet-to-tap" re-use programs) highlights the need for vastly improved approaches to risk communication.

- Highlights need for scientists to better convey the significance of their work to the public.
- Points to need for exploring more effective means for aligning the long-troubling disconnect of disparate views of risks as held by scientists versus the public: *real hazard vs. risk perception*.
- Receiving little attention is the more substantive role that could be played by the cognitive sciences (social scientists and psychologists) in helping to bridge the communications gap.

Key Role of Beliefs in Public Acceptance of Recycled Water

- Historically, some water re-use projects have become "branded" with negative images by consumers.

- Negative images cannot necessarily be erased or corrected by more or even better science. In fact, studies show that additional supportive data often serves to exacerbate already-formed negative images.

- Instead, we must involve social psychologists to bridge the communications gap between science and the public.

- The "yuck factor" associated with so-called "toilet-to-tap" programs, for example, derives from beliefs that have long been imbedded in social belief constructs, and these beliefs are refractory to being influenced by positive findings of science.

continued >

Confusion from Scientific Terminology

Is a ppm < or > than a ppb?

Mixing Ratios: Concentrations expressed on the "parts-per" basis

Whereas a scientist knows that:

ppt (o/oo) > ppm > ppb > ppt ,

the public often interprets the relative magnitudes of these concentrations in exactly the reverse, simply because it makes no sense that:

Thousand > Million > Billion > Trillion

So **the lower the concentration** of a toxicant reported by a chemist using the "parts-per" notation, **the higher can be the perceived risk** (because the focus is on the quantifiers and the "parts-per" is simply ignored).

Making things even more complicated is the fact that numbers larger than 10^9 do not have the same meanings worldwide; this is why NIST does not condone parts-per notation:
http://physics.nist.gov/Pubs/SP811/sec07.html#7.10.3

continued >

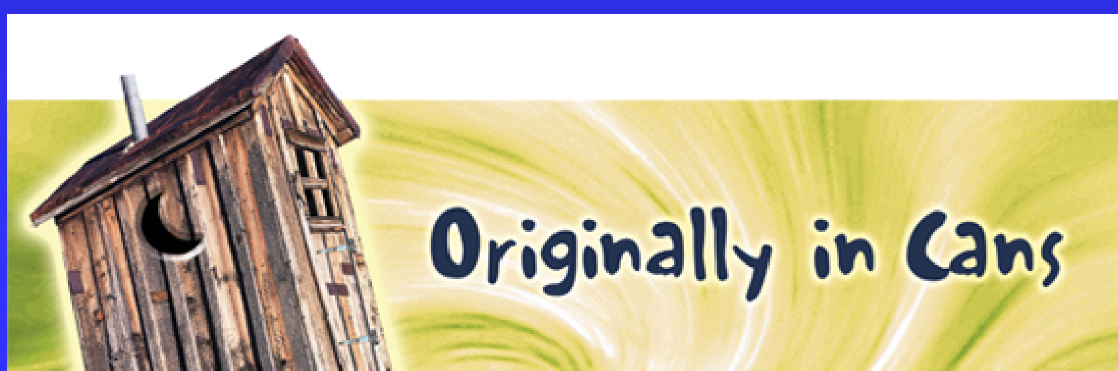
Risk Communication and Water Re-Use

An examination in new light of the problems with communicating risk, especially with regard to groundwater injection and water reuse:

Daughton C.G. "Groundwater Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds," In Fate and Transport of Pharmaceuticals and Endocrine Disrupting Compounds (EDCs) During Ground Water Recharge (special issue), *Ground Water Monitoring & Remediation*, **2004**, 24(2): 127-138.

http://www.epa.gov/nerlesd1/chemistry/ppcp/images/water-reuse.pdf

continued >



Real-world lesson in communicating:

<u>*Outhouse Springs*</u> Bottled Water

Experiment by: *Adams Outdoor Advertising*, South Carolina, 2002

http://www.outhousesprings.com/index.html

continued >

Advertising Wars between bottled water and tap:

"I don't drink the water I use (to flush).
I choose Cristaline"

Ad campaign of French bottled water company Groupe Neptune
January 2007: 1,400 billboards across Paris

concluded

Drug Disposal: The Key Questions Regarding Its Environmental Significance

- **What portion of environmental drug residues originate from direct disposal versus excretion and bathing?** This ratio is totally unknown.
- Does this fraction vary from drug to drug, or among packaging types (e.g., bulk bottles versus blister packs)?
- It is possible that direct disposal may indeed be a significant source of environmental residues for a limited number of drugs, such as for OTC medicines (especially those that are bulk purchased in such large quantities that they expire before being completely used). In contrast, disposal is probably not a significant source for those drugs provided by unit dispensing and for those that are costly or prescribed in short courses.
- It is quite possible, therefore, that even if environmentally sound drug disposal could be implemented, the resulting reduction in overall environmental loads of PPCPs might be negligible (at least for most drugs).

Drug Disposal – Other Issues

- Public identifies strongly with the topic and is concerned about the possibility for residues in drinking water.
- The way in which risk is perceived regarding chemical pollutants in drinking water is unrelated to actual concentrations (whether they are ppm or ppt). Chemicals that occur where they are neither expected nor desired are viewed as "chemical weeds" (Daughton 2005).
- For the first time (February 2007), a federal agency (ONDCP) has issued guidance regarding drug disposal. But much confusion exists at the local and state levels, primarily because of the number of disparate state and federal regulations that impact the issue.
- **Proper disposal is greatly complicated by the inherent, fundamental conflict between the need to protect public safety and the need to minimize aquatic exposure.**
- The major limitation in implementing drug “take-back” or “returns” programs is the Controlled Substances Act (as administered by the DEA).

PPCPs: *Pollution Reduction*

Numerous suggestions for a comprehensive pollution reduction program centered on environmental stewardship have been compiled in a two-part monograph published in *Environmental Health Perspectives 111*, 2003. This and other materials relevant to this topic are available here:

"How should unwanted/unneeded medications be disposed?"

http://epa.gov/nerlesd1/chemistry/pharma/faq.htm#disposal

Risk Communication and Water Re-Use

Society's perplexing relationship with the paradoxical simplicity and complexity of water is reflected perhaps in no better way than by DH Lawrence's *The Third Thing* (Pansies 1929):

Water is H20

Hydrogen two parts

Oxygen one

But there is a third thing

That makes it water.

And nobody knows what that is.

Inter-Organization Projects on Pharmaceuticals

Federal Interagency Task Group on Pharmaceuticals. Created in September 2004 by the White House's National Science and Technology Council's subcommittee on Health and the Environment (now Toxics and Risks). Co-chaired by the U.S. FDA, EPA, and USGS. Comprises representatives from the CDC, EPA, FDA, NIEHS, USDA, USGS, and NOAA. A major objective is to recommend how the various federal agencies having roles related to pharmaceuticals as environmental pollutants can prioritize research, better coordinate their efforts, and collaborate more effectively.

SETAC *Pharmaceutical Advisory Group* (PAG; formed at the World Council meeting in Portland, Fall 2004, by Dr. Hans Sanderson, Soap and Detergent Association, Washington, DC). Comprises subcommittees on: Environmental Effects; Chemical Fate & Predicted Environmental Concentrations; Water Treatment & Management; Environmental Risk Assessment; Future Criteria for Risk Management; Mixtures. Chaired by Rich Williams (Pfizer Inc). See: http://www.setac.org/pharmsag/

Some Possible Options for Next Steps

The Problem: How do we minimize the exposure hazards from waste streams to ensure the sustainability of a chemical-based, chemical-centric society in the most cost-effective manner?

Complicating Factors: Countless existing and yet-to-emerge non-regulated chemicals continually enter waste streams. Resources are sufficient only for monitoring a select few.

Partial Solution that Leverages its Impact via Collateral Outcomes: Regardless of whether PPCPs prove to pose hazards as trace environmental pollutants, actions directed at pollution prevention and pollution control could achieve much broader beneficial outcomes - - beyond PPCPs.

continued >

Collateral Benefits from Targeted Actions

(1) Collateral reduction in introduction of all consumer chemicals to waste streams via PPCP pollution prevention measures. [Educating the public to the fact that ALL of their actions, activities and behaviors can impact their environment.]

(2) Collateral reduction in removal of chemical pollution via PPCP pollution control measures. [Money spent in removing one class of pollutants is highly leveraged because it can also facilitate the removal of certain other pollutants - - even the "stealth" ones we don't yet know are present.]

(3) Reducing the necessity for monitoring a wide array of PPCPs by carefully selecting conservative surrogates (those most refractory to waste treatment processes). [Carbamazepine and iodinated X-ray contrast agents (e.g., iopromide) are widely used throughout society and are also refractory to conventional treatment technologies. Optimizing their removal could further enhance removal of others.]

continued >

Collateral Benefits from Targeted Actions *(cont'd)*

(4) Minimizing overall chemical hazard remaining after control measures by focusing monitoring resources on a select few of the most potent PPCPs (e.g., estrogens) or those that are less potent but which are introduced in much greater quantities (e.g., alkylphenols).

(5) Assessing overall hazard with a defined suite of biological assays based on evolutionarily conserved physiological processes whose responses integrate the signals from all chemical stressors present. Examples include cell-based assays for measuring inhibition of efflux pumps, endocrine modulation responses, and cellular stress responses.

Questions 

feel free to contact:

Christian Daughton, Ph.D.

Chief, Environmental Chemistry Branch

Environmental Sciences Division

National Exposure Research Laboratory

U.S. Environmental Protection Agency

daughton.christian@epa.gov

702-798-2207

http://www.epa.gov/nerlesd1/chemistry/pharma/


graphic prepared by:
C.G. Daughton, U.S. EPA
September 2002
Optical Photomicrographs of Crystalline Drugs
acetaminophen
fluoxetine
sildenafil
albuterol
ranitidine
caffeine
diazepam
for more photomicrographs of crystalline drugs, see:
© Molecular Expressions, Michael W. Davidson & The Florida State University Research Foundation
http://micro.magnet.fsu.edu

prepared for:

Pharmaceuticals and Personal Care Products Symposium

California Department of Toxic Substances Control
Sacramento, California
22 May 2007

Christian Daughton, Ph.D.

Chief, Environmental Chemistry Branch
Environmental Sciences Division
National Exposure Research Laboratory
U.S. Environmental Protection Agency
daughton.christian@epa.gov
702-798-2207

prepared: 6 April 2007